- wherein L is a linker selected from propargyl-ethyl-oxide-amino and propargylamino wherein the linker is attached to the 8-C of a adenine, 7-deazaadenine, guanine, or 7-deazaguanine nucleobase, the 7-C or 8-C of a 7-deazaadenine or 7-deazaguanine nucleobase, or the C-5 of a uracil or cytosine nucleobase; and

- wherein Dye is selected from a rhodamine dye and a fluorescein dye; and

125. (New) The method according to claim 101, wherein the reporter group is a rhodamine-type dye, a fluorescein-type dye, an energy transfer dye, or a cyanine-type dye.

126. (New) The method according to claim 101, further comprising separating the fragments that contain at least one primer from other fragments.--

REMARKS

With entry of this Amendment, claims 1-118, 120, 121, and 123-126 are pending in this application. The Office has withdrawn claims 1-100 and 115-123 from consideration. Claims 101-114 were examined in the Office Action mailed January 31, 2003. Claims 101-114 stand rejected.

The Claims Are Definite

Claims 101-114 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for their recitation of "at least one dye-labeled ribonucleotide of the invention." (Office Action, page 2.)

As suggested by the Examiner, Applicants have amended claim 101 to recite "at least one dye-labeled ribonucleotide having the formula" of as-filed claim 1. Because

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compounds having this formula are the dye-labeled ribonucleotides of the invention, this amendment does not change the scope of claim 101 and does not add new matter. In addition, Applicants have added dependent claims 124 and 125, which recite specific embodiments of the formula of amended claim 101, and claim 126, which recites an additional step. The newly added claims are supported by the as-filed claims and add no new matter.

Applicants respectfully request the withdrawal of the rejection of claims 101-114 under 35 U.S.C. § 112, second paragraph.

The Claims Are Not Obvious

Claims 101-114 are also rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 6,500,650 to Stanton et al. ("Stanton") in view of Rosenblum et al., Nucl. Acids Res. 25: 4500-4504, 1997 ("Rosenblum"). (Office Action, pages 3-7.) According to the Office, Stanton "relates to a method for detecting a variance in a nucleotide sequence among related polynucleotides by replacing a natural nucleotide in a polynucleotide at substantially each point of incorporation of the natural nucleotide with a modified nucleotide at substantially each point of incorporation of the modified nucleotide, determining the mass of the fragments obtained and then comparing the masses with those expected from a related polynucleotide of known sequence or, if the sequence of a related polynucleotide is unknown, by repeating the above steps with a second related polynucleotide and then comparing the masses of the fragments obtained from the two related polynucleotides." (Office Action, pages 3-4.) The Office also asserts that Stanton discloses: 1) methods for isolating polymerases that incorporate modified nucleotides, 2) that the analysis may be

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performed on PCR extension products with or without purification, 3) that a detectable label may be incorporated, for example, in the extension primer or the extension product, and 4) that the labeled fragments may be identified by hybridization to an oligonucleotide. (*Id.*, pages 4-6.)

The Office states that "Rosenblum describes new dye labeled terminators for improved DNA sequencing patterns." (*Id.*, page 7.) According to the Office, it would have been obvious "to use the dye-labels of Rosenblum for the method of Stanton." (*Id.*)

Applicants respectfully traverse. In order to establish a *prima facie* case of obviousness under 35 U.S.C. § 103(a), the Examiner must establish three elements. First, the Examiner must point to a suggestion or motivation, either in the prior art or in the general body of knowledge, to modify or combine the prior art. Second, there must be a reasonable expectation of success in making the suggested modification. Third, the prior art as modified or combined must teach or suggest all limitations of the claimed invention. *See In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991); M.P.E.P. 2142.

As an initial matter, none of the alleged disclosures in Stanton relied on by the Office are methods for determining the sequence of a DNA template as recited by claims 101-114. Instead, as indicated by the abstract of Stanton:

> The present invention relates to methods for the detection of polymorphism in polynucleotides by using hybridization of fragments of a polynucleotide suspected of containing a polymorphism with an oligonucleotide having a sequence complementary to a fragment identifying the polymorphism and subsequent detection of the incorporated labels in the oligonucleotide-fragment duplex.

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In fact, the abstract describes the method recited by Stanton's claim 1, the only independent claim, and by the specification at, for example, col. 12, lines 27-62. Thus, the method relied on by the Office relates, not to DNA sequencing, but rather to determining whether a polymorphism, generally a single nucleotide change, is present in a DNA sample. In other words, the sequence of the sample *is not* determined, but whether or not a particular nucleotide is present at a specific site *is* determined.

In a portion of Stanton not relied on by the Office, Applicants note that a method for sequencing is proposed. *See* col. 57, lines 9-24. Stanton states, however, that his method requires four separate sequencing reactions, one separate experiment for each nucleotide. *See id.* In contrast, the methods of claims 101-114 permit a complete sequencing reaction to be performed and, for at least that reason, are different from the method of Stanton. Thus, Stanton fails to teach or suggest the method of determining the sequence of a DNA template recited in claims 101-114.

Moreover, the dye-labeled terminators disclosed by Rosenblum would not be useful in Stanton's method. The nucleotide analogs disclosed by Rosenblum are dideoxynucleotides the incorporation of which results in termination of the primer extension reaction. Stanton, in contrast, employs nucleotide analogs that do not terminate the primer extension reaction. *See, e.g.,* col. 12, lines 27-37. In fact, Stanton's methods are incompatible with a nucleotide analog that causes the primer extension reaction to terminate. Nor has the Office pointed to any teaching or suggestion that the dye-labels of Rosenblum could be linked to ribonucleotides to produce the dye-labeled ribonucleotides of Applicants' invention or that such compounds would be useful in the methods of Stanton.

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In summary, the Office has identified a method that uses cleavable nucleotide analogs to test for polymorphisms in one reference and a second reference that discloses dye-labeled dideoxynucleotide chain terminators and combined those references to reject claims drawn to a method for DNA sequencing using dye-labeled ribonucleotide analogs. This approach is flawed because (1) Stanton fails to teach or suggest a method for determining the sequence of a DNA template and Rosenblum does nothing to remedy this deficiency, (2) there exists no motivation to combine the references (as noted above, Stanton actually teaches away from this combination), and 3) there exists no reasonable expectation of success from combining the references. Applicants respectfully submit that the Office has impermissibly used Applicants' own disclosure as a blueprint for combining the prior art. *See In re Dembiczak*, 50 U.S.P.Q.2d 1614 (Fed. Cir. 1999). It is further noted that Stanton, whose earliest filing date is approximately one year *after* Rosenblum was published, failed to note the teachings of Rosenblum, which provides compelling evidence that one skilled in the art would not have made the combination relied on by the Examiner.

For the above reasons, Applicants request the reconsideration and withdrawal of the rejection of claims 101-114 under 35 U.S.C. § 103(a).

A Revised Oath/Declaration Is Provided

The Office noted that the original Oath/Declaration did not state that the person making the oath or declaration had reviewed and understood the contents of the specification, including the claims, as amended by any amendment specifically referred to in the oath or declaration. (Office Action, page 2.)

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Applicants now submit a revised Oath/Declaration in which the inventors make the required representation.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our Deposit Account No. 06-0916.

Respectfully submitted,

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Dated: June 2, 2003

By: 
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APPENDIX TO AMENDMENT OF APRIL 30, 2003

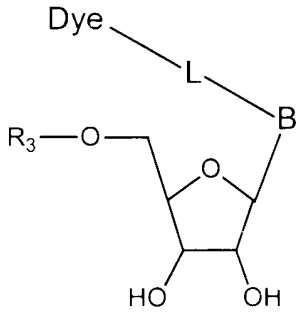
Amendments to the Claims

Insertions are shown double-underlined. Deletions are shown bracketed.

101. A method for determining a polynucleotide sequence [the sequence of a DNA template], comprising

(i) annealing at least one [oligonucleotide] primer to a template polynucleotide;

(ii) [incubating] extending said at least one [oligonucleotide] primer [with a DNA polymerase that can incorporate both dNTPs and rNTPs in a reaction comprising] in the presence of a mixture of unlabeled dNTPs and at least one dye-labeled ribonucleotide [of the invention] having the formula:



wherein B is a nucleobase; L is a linker; R_3 is triphosphate, α-thiotriphosphate, or a salt thereof, and Dye is a reporter group;

so that primer extension products that contain at least one dye-labeled ribonucleotide are formed;

(iii) [treating the] cleaving one or more primer extension products [with a means for hydrolyzing the extension products at each occurrence of a ribonucleotide] to form a plurality of labeled fragments;

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[(iv) separating the resulting fragments that contain said at least one primer from other fragments,]

[(v)] (iv) [resolving] separating the [primer-containing] extension products by size; and

[(vi)] (v) detecting the fragments to determine the polynucleotide sequence.

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